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Case Report

Prenatal diagnosis and molecular cytogenetic characterization of mosaicism for a small supernumerary marker chromosome derived from chromosome 21q11.2-q21.1 and a literature review

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ABSTRACT

Objective: We present prenatal diagnosis and molecular cytogenetic characterization of mosaicism for a small supernumerary marker chromosome (sSMC) derived from chromosome 21q11.2-q21.1, and we review the literature of an sSMC(21) with a duplication of 21q11.2-q21.1.
Case report: A 40-year-old woman underwent amniocentesis at 17 weeks of gestation because of advanced maternal age. Amniocentesis revealed a karyotype of 47,XX,+mar [18]/46,XX [4]. The parental karyotypes were normal. Prenatal ultrasound findings were unremarkable. aCGH analysis of cultured amniocytes revealed a 2.855-Mb duplication of 21q11.2-q21.1 encompassing the genes of *LIPI*, *ABCC13* and *NRIP1*. Metaphase fluorescence *in situ* hybridization analysis on cultured amniocytes revealed a result of 47,XX,+mar .ish der(13/21) (D13/21Z1+) [10]. Spectral karyotyping analysis determined the origin of chromosome 21 in the sSMC. A female fetus was delivered with no phenotypic features of Down syndrome and no structural abnormalities. We discuss the genotype–phenotype correlation of *LIPI*, *ABCC13* and *NRIP1*, and review the literature of an sSMC(21) associated with dup(21)(q11.2q21.1).
Conclusion: aCGH is useful for identification of the nature and genetic component of a prenatally detected sSMC.

Introduction

A small supernumerary marker chromosome (sSMC) is an extra chromosome that has a size equal to or smaller than a chromosome 20 and cannot be identified by conventional cytogenetic technology [1–3]. An sSMC derived from a non-acrocentric chromosome carries a higher risk for phenotypic abnormalities than an sSMC derived from an acrocentric chromosome (28% vs. 7%) [4]. We previously reported prenatal diagnosis and molecular cytogenetic characterization of an sSMC derived from chromosome 21 [5]. We previously also reported the application of array comparative genomic hybridization (aCGH) in identification of the nature and genetic component of an sSMC [6,7]. Here, we present an additional case of prenatal diagnosis of an sSMC(21) with euchromatic

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material detected by aCGH. We also review the literature of an sSMC(21) with a duplication of chromosome 21q11.2-q21.1.

Case report

A 40-year-old woman, gravid 2, para 1, underwent amniocentesis at 17 weeks of gestation because of advanced maternal age. Her husband was 44 years old. The woman and her husband were normal, and there was no family history of congenital malformations. Amniocentesis revealed a karyotype of 47,XX,+mar [18]/46,XX [4]. Among 22 colonies of cultured amniocytes, 18 colonies had a karyotype of 47,XX,+mar (Fig. 1), whereas the rest four colonies had a karyotype of 46,XX. The parental karyotypes were normal. Prenatal ultrasound findings were unremarkable. aCGH analysis of cultured amniocytes by SurePrint G3 Unrestricted CGH ISCA v2, 8 × 60 K Array (Agilent Technologies, Santa Clara, CA, USA) revealed a result of arr 21q11.2-q21.1 (15,485,008–18,340,054) × 3.0 with a 2.855-Mb duplication encompassing 10 Online Mendelian Inheritance of in Man (OMIM) genes of *LIPI*, *ABCC13*, *HSPA13*, *SMASN1*, *NRIP1*, *USP25*, *MIR99AHG*, *MIR99A*, *MIRLET7C* and *MIR125B2* (Fig. 2). Metaphase fluorescence *in situ* hybridization (FISH) analysis on cultured amniocytes revealed a result of 47,XX,+mar .ish der(13/21)(D13/21Z1+) [10] (Fig. 3). Spectral karyotyping (SKY) analysis determined the origin of chromosome 21 in the sSMC (Fig. 4). The parents elected to terminate the pregnancy, and a female fetus was delivered with no phenotypic features of Down syndrome and no structural abnormalities. aCGH analysis of the DNA extracted from the skin revealed a result of arr 21q11.2-q21.1 (15,485,008–18,340,054) × 3.0. Cytogenetic analysis of the chrorionic villi revealed a karyotype of 47,XX,+mar[27]/46,XX [13].

Discussion

The present case had an sSMC(21) with a duplication of 21q11.2-q21.1 without involving Down syndrome critical region of 21q22.13~q22.3 and presented no Down syndrome phenotype. Capkova et al. [8] reported a 4-year-old boy with hypotonia, brachycephaly, sandal gaps, joint hyperlaxity, developmental delay and speech delay with partial trisomy 21q11.2-q21.3, and a 6-year-old boy with macroglossia, hypotonia, joint hyperlaxity and normal mental development with partial tetrasomy 21q11.2 and partial trisomy 21q11.2-q21.3. To date, at least eight cases with an sSMC(21) and a partial duplication encompassing 21q11.2-q21.1 have been reported of which three cases are without clinical findings, and five cases are with clinical findings [2,9–14]. Liehr et al. [2] reported prenatal diagnosis of mosaicism for an sSMC(21) derived from 21p11.2-q21.1 and a phenotypically normal boy at one year of age. Liehr [14] reported a supernumerary r(21)(::p11.2 → q21.1::) in a normal female and her unborn child. Polityko et al. [10] reported a supernumerary r(21)(::p11.2 → q21.1::) in a normal male of whom the female partner had reported abortions. Liehr [14] reported 25% (5/20) mosaicism for an sSMC(21) derived from 21pter-q21.1 in the blood of a 62-year-old male with psychomotor retardation, severe developmental delay, no sexual development, short stature and microcephaly. Hamid et al. [13] and Liehr [14] reported 33.3% (5/15) mosaicism for an sSMC(21) derived from 21pter-q21.1 in the blood of a 4-year-old male with scoliosis, depressed nasal bridge, delayed fine motor skills and autism. Viersbach et al. [9] reported 70% mosaicism for a supernumerary r(21)(p11.2q21) in the blood of a 7-year-old female with facial dysmorphism, hypotonia and slightly developmental retardation. Baldwin et al. [11] reported 75% mosaicism for an sSMC(21) derive from 21pter → q21.1 in a 19-year-old individual with borderline normal intelligence, mild facial dysmorphism, bipolar disorder and diabetes mellitus. Liehr [14] reported 11.3% (6/53) mosaicism for an sSMC(21) derived from 21pter-q21.1 in the blood of an 8-year-old female with seizures, regression and mental retardation.

The present case had a duplication of 21q11.2. Niikawa et al. [15] and Shen et al. [16] mapped the putative transient abnormal myelopoiesis (*TAM*) gene at 21q11.2. TAM or transient myeloproliferative syndrome (OMIM 159595) is a leukemoid reaction that may occur in the newborn infants with Down syndrome [17]. The

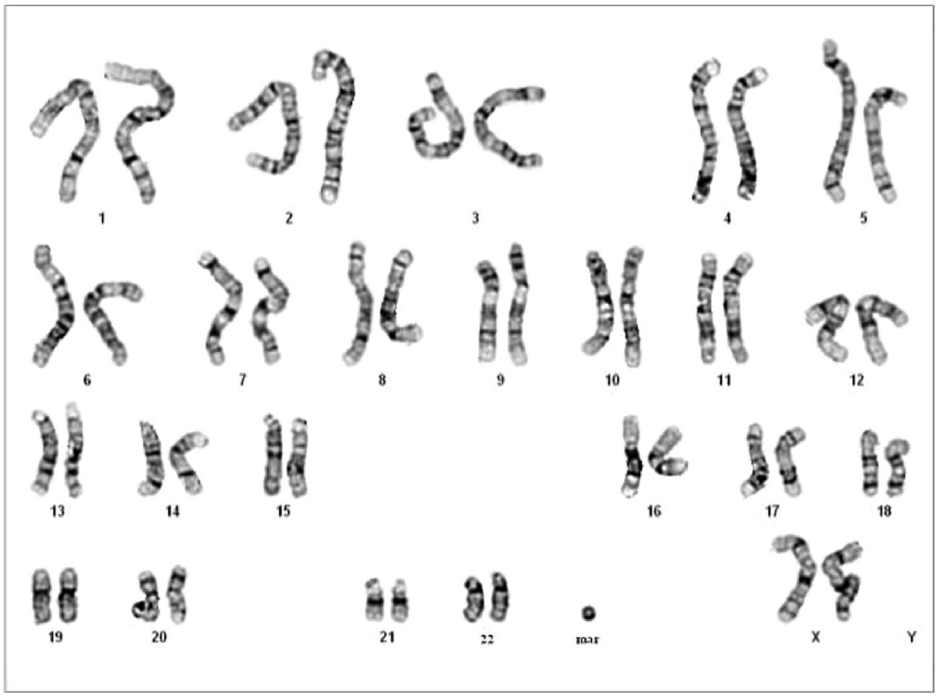

Fig. 1. A karyotype of 47,XX,+mar. mar = marker chromosome.

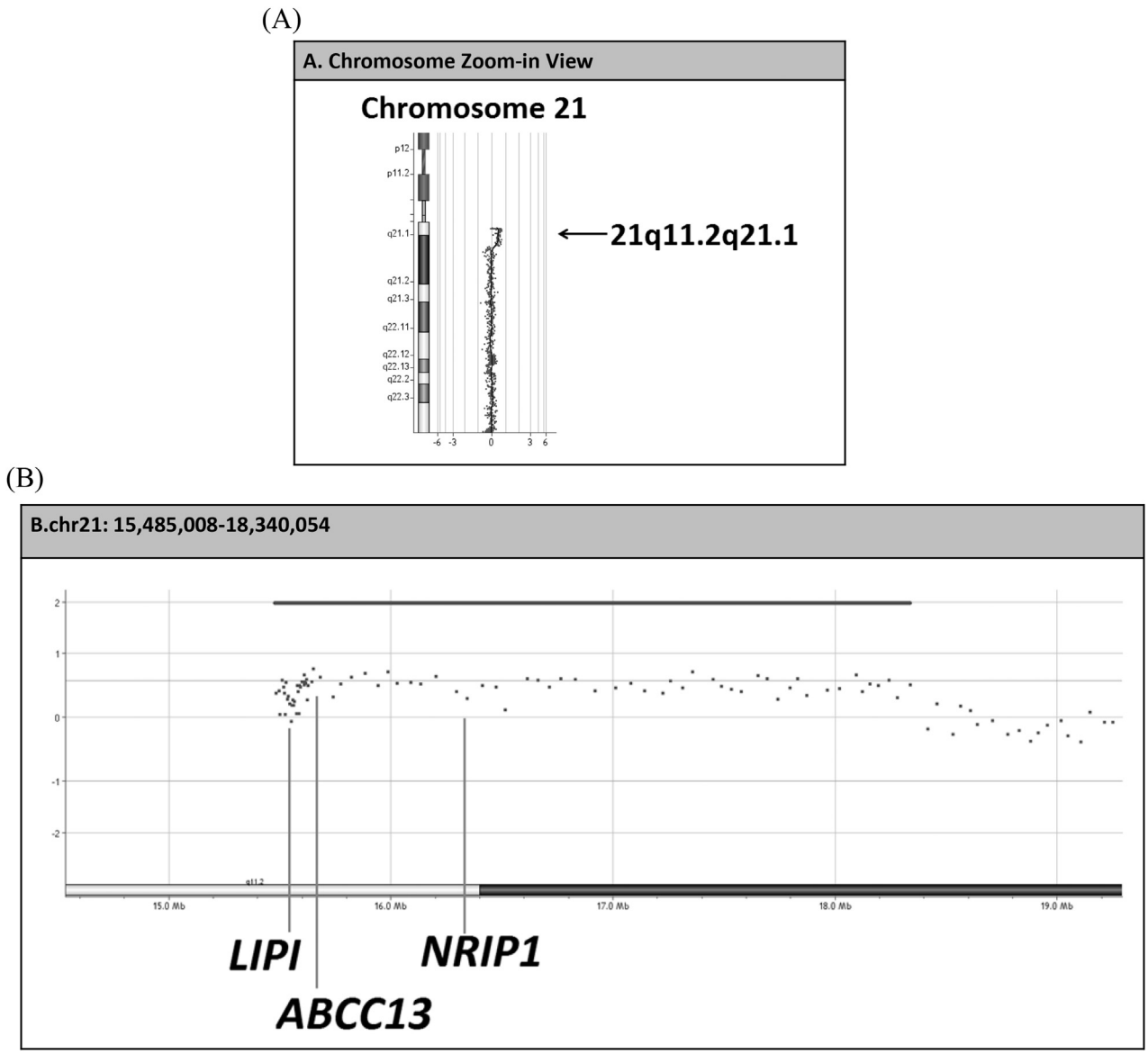

Fig. 2. Array comparative genomic hybridization analysis on cultured amniocytes shows a 2.855-Mb duplication of 21q11.2-q21.1 encompassing the genes of *LIPI*, *ABCC13* and *NRIP1*. (A) and (B) chromosome 21 zoom-in views.

present case had a 2.855-Mb duplication of 21q11.2-q21.1 encompassing *LIPI*, *ABCC13* and *NRIP1*. Mutations of *LIPI* (OMIM 609252) are associated with autosomal dominant susceptibility to hypertriglyceridemia (OMIM 145750) [18]. Single nucleotide polymorphisms (SNPs) in *ABCC13* (OMIM 608835) have been associated with non-word repetition and reading measures [19]. *NRIP1* (OMIM 602490) is located at 21q11.2-q21.1 and encodes the transcriptional coregulator of receptor-interacting protein 140 (RIP140) or nuclear receptor-interacting protein 1 (NRIP1). NRIP1 or RIP140 is involved in the regulation of various oncogenic signaling pathways and participates in the development and progression of solid tumors and chronic lymphocytic leukemia [20]. Over-expression of NRIP1 is associated with psoriasis [21]. NRIP1 over-expression in Down syndrome down-regulates peroxisome proliferator-activated receptor γ, coactivator 1α (*PGC-1*α or *PPARGC1A*) and nuclear-encoded mitochondrial genes (NEMGs), and causes mitochondrial dysfunction in Down syndrome [22].

In summary, we present prenatal diagnosis and molecular cytogenetic characterization of mosaicism for an sSMC(21) derived from chromosome 21q11.2-q21.1. Our presentation demonstrates

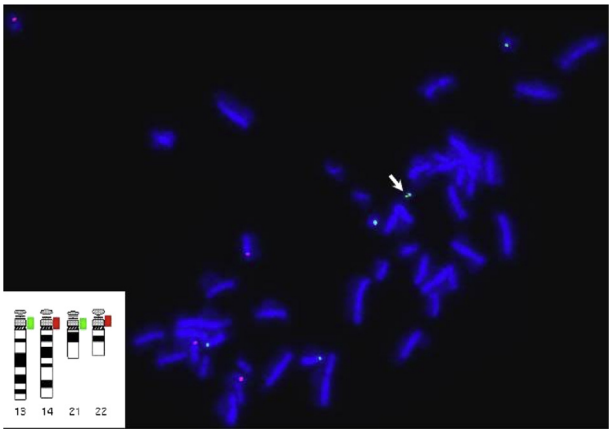

Fig. 3. Metaphase fluorescence *in situ* hybridization analysis using the CEP13/21 FISH probe (D13/21Z1; spectrum green) and the CEP14/22 FISH probe (D14/22Z1; spectrum red) (Cytocell Inc, Adderbury, Oxfordshire, UK) shows four red signals and five green signals. The marker chromosome (arrow) presents a green signal indicating that the marker chromosome is derived from chromosome 13/21.

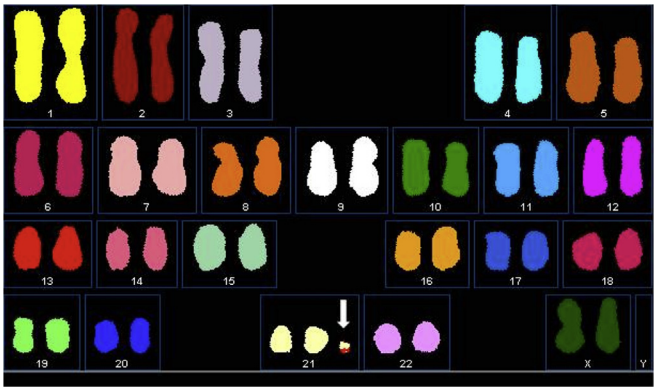

Fig. 4. The spectral karyotyping (SKY) analysis using 24-color SKY probes (Applied Spectral Imaging, Carlsbad, CA, USA) shows that the small supernumerary marker chromosome (arrow) is derived from chromosome 21.

the usefulness of aCGH in the identification of the nature and genetic component of a prenatally detected sSMC.

Conflict of interest

The authors have no conflicts of interest relevant to this article.

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